

# THE EXPERIMENTAL RESEARCH ON THE ANTI-INFLAMMATORY ACTION OF THE NEW PIROXICAM-CAFFEINE PHARMACEUTICAL COMPOSITION

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**Abstract.** *Conducting an experimental research on laboratory rats subjected to endogastric injections, our scientists have explored the influence of the non-steroid anti-inflammatory drug from the oxicam group piroxicam (4-hydroxo-2-methyl-N-pyridine-2-il)-2H-1,2-benzothiazine-3-carboxamide1,1-dioxyde), a well-known adjuvant of non-narcotic analgetics and non-steroid anti-inflammatory drugs such as caffeine (1,3,7-trimethylxanthine) and the two-component piroxicam-caffeine pharmaceutical composition on the rats' anti-exudative activity under formalin edema.*

*The analysis of the results of the experimental researches points to the fact that caffeine promotes the anti-exudative action of piroxicam in the rats under formalin edema. The above-mentioned experimental researches allow us to come to the conclusion that due to its vasoconstrictive effect caffeine performs as an adjuvant to piroxicam (a non-steroid anti-inflammatory drug from the oxicam group) concerning the anti-exudative activity.*

*The results of the research can become a basis for the development of new combined drugs in Ukraine.*

**Keywords:** *piroxicam, caffeine, pharmaceutical composition, anti-inflammatory effect, formalin edema.*

**Introduction.** The pharmacological action of a drug is determined by the nature and strength of its bond with the structure of the target in a body, which, in turn, depends on the molecular parameters. Therefore, our previous researches, first of all, were focused on studying the quantum chemical properties of such well-known non-steroid anti-inflammatory drugs (NSAIDs) and non-narcotic analgetics (NNA) of the different chemical structure as: paracetamol, ibuprofen, diclofenac, piroxicam and others [1-6]. Our previous researches on caffeine, a famous adjuvant of NSAIDs [7-9], determined its properties as an adjuvant [10-30].

According to the quantum chemical researches on caffeine, oxygen and nitrogen atoms are the basic reaction centers of its molecule, tinting and building hydrogen bonds. A caffeine molecule is a soft reagent, actively interacting with lye amino acids, non-saturated and aromatic compounds [8, 9]. The quantum chemical researches of caffeine allow us to make an assumption that its potentiating action towards NSAIDs and NNA is predetermined by the molecular geometric and electronic characteristics, promoting the bioavailability of anti-inflammatory drugs and analgetics [10, 11, 16-30].

The previous experimental researches, conducted at the Department of Medical and Bioorganic Chemistry studying the anti-exudative, analgetic, antipyretic action of the well-known NSAIDs of the different chemical structure (paracetamol, diclofenac sodium, ibuprofen) with caffeine, have shown that the latter potentiates the anti-exudative, analgetic activity of the NSAIDs under study [11, 19-30]. Moreover, it has been found that caffeine increases and prolongs the anti-exudative effect of paracetamol [11-30].

Caffeine is known to potentiate the pharmaceutical action of NSAIDs and NNA in combined drugs [10-16]. However, there are no oxicam-caffeine compositions in the world practice. Therefore, piroxicam as a representative of this pharmaceutical group has been chosen by us as an object of future researches. Deriving from pyridine-2-ilamid, this medicament, apart from its anti-inflammatory action, is characterized by a rather distinctive analgetic activity and used to treat rheumatic diseases, nerve pains, a post-traumatic pain syndrome and other diseases [31-36].

Taking into consideration the above-stated information, we find it appropriate to pursue a research on the anti-exudative effect of the caffeine-piroxicam pharmaceutical composition comparing to their mono-injections.

**Materials and methods.** An experimental research has been conducted to study the specific action of oxicam (piroxicam), caffeine and their two-component pharmaceutical composition. Diclofenac sodium, a well-known NSAID, has been chosen as a reference agent.

The anti-exudative action of the drugs under research and their pharmaceutical composition has been studied on white male rats of the WAG line with an average weight of 200-240g by means of the formalin edema experimental pattern as compared to the diclofenac sodium reference agent [37]. The edema was designed by giving the 0,1 ml 2 % formalin solution sub-plantar injection to the hinder limb of the animal. The volume of the limb was measured by the IITS Life Science (USA) plethysmometer (prior to the formalin modeling injection and 4 hours after injecting phlogogen (formalin) at the peak of the edema [37].

The animals were divided into 6 groups with 6 animals in each group. The animals of the 1<sup>st</sup> group as a control group were administered a single oral endogastric injection of 3 % starch mucus (2 ml per 200g of the animals' weight). Formalin edema was modeled in the animals of group 2 by giving them a 2 % formalin sub-plantar injection and a 3 % starch mucus endogastric injection into their hinder limbs [37]. As a 3 % starch mucus suspension, single endogastric injections of the above-mentioned drugs under research and their compositions were given to the specimens from groups 3<sup>th</sup> through 6 in the following way: the animals from group 3<sup>th</sup> were injected with piroxicam, dosing 1,3mg per 1kg of the animals' weight, group 4<sup>th</sup> was injected with caffeine (0,6 mg/kg), the 5<sup>th</sup> group was injected with the piroxicam (1,3mg/kg)-caffeine (0,6mg per 1kg of the animals' weight) combination and the 6<sup>th</sup> group was injected with diclofenac sodium (8mg/kg). The peak of formalin edema being observed 4 hours after its modeling [37], the drugs, as well as 3 % starch mucus, were injected an hour before that. Doses for human beings were recalculated into those for the rats by applying the species sensitivity coefficient according to Rybolovlev Y.R. [38].

The edema enlarging was determined with the help of milliliters (ml). The percentage of inflammation suppression was calculated by the following formula:

$$\% \text{ inflammation suppression} = \frac{V_c - V_e}{V_c} \cdot 100\% , \quad (1)$$

with  $V_c$  – the volume of the limb in the control specimen minus the initial volume of this limb prior to edema, ml;

$V_e$  – the volume of the limb, swollen during the experiment, minus the initial volume of this limb, ml.

**Results and discussions.** Modelling formalin edema enlarged the volume of the animals' limbs by 34 %. Piroxicam injection under formalin edema suppressed the edema by 44,44 %, making no statistically relevant difference from the reference agent (44,00 %). Caffeine mono-injection suppressed the edema by 18,33 %. The application of caffeine to the oxicam under research promoted the anti-exudative activity by 61,11 %.

The results of the research on the anti-exudative action of the medicaments and their pharmaceutical compositions are given in table 1.

Table 1. The experimental research on the anti-exudative action of piroxicam, caffeine and its pharmaceutical composition in rats under formalin edema (n=6)

| №  | Animals' groups              | The volume of a rat's limb at the onset of the experiment, ml | The volume of a rat's limb after 4 hours the experiment, ml | Anti-exudative activity, % |
|----|------------------------------|---------------------------------------------------------------|-------------------------------------------------------------|----------------------------|
| 1. | Control                      | 0,57±0,01                                                     | 0,57±0,01                                                   |                            |
| 2. | Formalin edema (f. e.)       | 0,58±0,01                                                     | 0,76±0,03*/***/*****/*****                                  |                            |
| 3. | Piroxicam (f. e.)            | 0,55±0,03                                                     | 0,65±0,02*/**/****                                          | 44,44                      |
| 4. | Caffeine (f. e.)             | 0,58±0,01                                                     | 0,73±0,01*/***/*****/*****                                  | 18,33                      |
| 5. | Piroxicam + caffeine (f. e.) | 0,56±0,02                                                     | 0,63±0,01*/**/****                                          | 61,11                      |
| 6. | Diclofenac sodium (f. e.)    | 0,57±0,01                                                     | 0,67±0,01*/**/****                                          | 44,00                      |

Remarks (average ± error of mean):

\* - the results validity as related to the control group,  $P < 0,05$ ;

\*\* -the results validity as related to f. e.,  $P < 0,05$ ;

\*\*\* - the results validity as related to piroxicam mono-injection,  $P < 0,05$ ;

\*\*\*\* - the results validity as related to caffeine mono-injection,  $P < 0,05$ ;

\*\*\*\*\* - the results validity as related to composition caffeine-piroxicam injection,  $P < 0,05$ ;

\*\*\*\*\* - the results validity as related to diclofenac sodium mono-injection,  $P < 0,05$ ;

The piroxicam-caffeine composition demonstrated the suppression of the edema by 61,11 %, thus considerably surpassing the anti-exudative activity of diclofenac sodium as a reference medical agent. It means, caffeine effectively potentiated the anti-exudative activity of piroxicam, probably, due to its vasoconstrictive effect, observed by us in our previous researches on the NSAIDs of the different chemical structure [12, 17, 23, 29].

**Conclusions.** 1. The medical agents under research, piroxicam, caffeine and their pharmaceutical composition showed a distinctive anti-exudative action in the rats under formalin edema. Piroxicam injection under formalin edema suppressed the edema by 44,44 %, thus equalling the injection of diclofenac sodium as a reference agent. Caffeine application to the oxicom under research boosted the anti-exudative action in piroxicam by 61,11 %.

2. The experimental and biochemical researches, conducted by us, allow us to conclude that caffeine due to its vasoconstrictive effect, observed by us in our previous researches on NSAIDs of the different chemical structure, serves as an adjuvant to the oxicom concerning the anti-exudative action.

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